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## YAP Induces Human Naive Pluripotency.

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### Public Summary:

This study reports the discovery that early human pluripotent stem cells can be grown in specific conditions and depend on a gene called YAP for their propagation. Unlike standard human pluripotent stem cells, these "naive" pluripotent stem cells are very straightforward to grow in the lab, which will greatly facilitate the development of novel strategies in regenerative medicine.

### Scientific Abstract:

The human naive pluripotent stem cell (PSC) state, corresponding to a pre-implantation stage of development, has been difficult to capture and sustain in vitro. We report that the Hippo pathway effector YAP is nuclearly localized in the inner cell mass of human blastocysts. Overexpression of YAP in human embryonic stem cells (ESCs) and induced PSCs (iPSCs) promotes the generation of naive PSCs. Lysophosphatidic acid (LPA) can partially substitute for YAP to generate transgene-free human naive PSCs. YAP- or LPA-induced naive PSCs have a rapid clonal growth rate, a normal karyotype, the ability to form teratomas, transcriptional similarities to human pre-implantation embryos, reduced heterochromatin levels, and other hallmarks of the naive state. YAP/LPA act in part by suppressing differentiation-inducing effects of GSK3 inhibition. CRISPR/Cas9-generated YAP(-/-) cells have an impaired ability to form colonies in naive but not primed conditions. These results uncover an unexpected role for YAP in the human naive state, with implications for early human embryology.

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